UNIVERSITY OF HELSINKI

https://helda.helsinki.fi

# Trends in MDMA-related mortality across four countries

**Roxburgh, Amanda; Sam, Bulent; Kriikku, Pirkko; Mounteney, Jane; Castanera, Antonio ...**

**2021-11**
Wiley Blackwell
http://hdl.handle.net/10138/353480
Roxburgh, A, Sam, B, Kriikku, P, Mounteney, J, Castanera, A, Dias, M & Giraudon, I 2021, 'Trends in MDMA-related mortality across four countries', Addiction, vol. 116, no. 11, pp. 3094-3103. https://doi.org/10.1111/add.15493

Downloaded from Helda, University of Helsinki institutional repository. https://helda.helsinki.fi
This is an electronic reprint of the original article.
This reprint may differ from the original in pagination and typographic detail.
Please cite the original version.

*"This is the peer reviewed version of the following article:* Roxburgh, A., Sam, B., Kriikku, P., Mounteney, J., Castanera, A., Dias, M., and Giraudon, I. (2021) Trends in MDMA-related mortality across four countries. *Addiction, 116: 3094– 3103. , which has been published in final form at https://doi.org/10.1111/add.15493.*

*This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Use of Self-Archived Versions. This article may not be enhanced, enriched or otherwise transformed into a derivative work, without express permission from Wiley or by statutory rights under applicable legislation. Copyright notices must not be removed, obscured or modified. The article must be linked to Wiley's version of record on Wiley Online Library and any embedding, framing or otherwise making available the article or pages thereof by third parties from platforms, services and websites other than Wiley Online Library must be prohibited."*

# Trends in MDMA-related mortality across four countries

Amanda Roxburgh[1,2,3], Bulent Sam[4], Pirkko Kriikku[5,6], Jane Mounteney[7], Antonio Castanera[8], Mario Dias[8,9], and Isabelle Giraudon[7,10]

1. Behaviours and Health Risks Program, Burnet Institute, Melbourne, Australia
2. Discipline of Addiction Medicine, the Central Clinical School, Sydney Medical School, the Faculty of Medicine and Health, University of Sydney, Sydney, Australia
3. National Drug and Alcohol Research Centre, UNSW, Sydney, Australia
4. Member of the Council of Mortality Related Cases, the Council of Forensic Medicine of Ministry of Justice, Turkey
5. Forensic Toxicology Unit, Finnish Institute for Health and Welfare, Helsinki, Finland
6. Department of Forensic Medicine, University of Helsinki, Helsinki, Finland
7. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), Lisbon, Portugal
8. Serviço de Quimica e Toxicologia Forenses do Instituto Nacional de Medicina Legal e Ciências Forenses, Lisboa, Portugal
9. Laboratório de Ciências Forenses e Psicológicas Egas Moniz, Almada, Portugal
10. University NOVA and National School of Public Health, Lisbon, Portugal

**Conflict of interest declaration:** None.

**Correspondence:** Dr Amanda Roxburgh
Phone: +61 (0) 407 573 576
E-mail: amanda.roxburgh@burnet.edu.au

**Word Count:** 3,675

**Running head:** MDMA-related deaths in Australia and selected European countries

**Keywords:** MDMA, drug-related deaths, Ecstasy, Mortality, Toxicity, Toxicology.

**Abstract**

*Aims:* To determine trends in 3,4 methylenedioxymethamphetamine (MDMA)-related death rates across Australia, Finland, Portugal and Turkey and to analyse causes of death across countries; and 3. analyse the toxicology of deaths across countries.

*Design:* Analysis of MDMA-related deaths extracted from a national coronial database in Australia (2001-2019) and national forensic toxicology databases in Finland (2001-2017), Portugal (2008-2019) and Turkey (2007-2017). Presentation of MDMA use and seizure data (market indicators).

*Setting:* Australia, Finland, Portugal and Turkey.

*Cases:* All deaths in which MDMA was considered by the forensic pathologist to be contributory to death.

*Measurements:* Information collected on cause and circumstances of death, demographics, and toxicology.

*Findings:* 1,400 MDMA-related deaths were identified in Turkey, 507 in Australia, 100 in Finland, and 45 in Portugal. The median age ranged from 24 to 27.5 years and males represented between 81 and 95% of the deaths across countries. Standardised mortality rates significantly increased across all four countries from 2011-2017, during a period of increased purity and availability of MDMA. The underlying cause of death was predominantly due to drug toxicity in Australia (n=309, 61%), Finland (n=70, 70%) and Turkey (n=840, 60%), and other causes in Portugal (n=25, 56%). Minorities of all deaths across the countries were due to MDMA toxicity alone (13-25%). These deaths had a significantly higher blood MDMA concentration than multiple drug toxicity deaths in Australia, Finland and Turkey. Drugs other than MDMA commonly detected were stimulants (including cocaine, amphetamine and methamphetamine) (Australia - 52% and Finland 61%) and alcohol (Australia - 46% and Portugal 49%). In addition to MDMA toxicity, benzodiazepines (81%) and opioids (64%) were

commonly identified in these deaths in Finland. In comparison, synthetic cannabinoids (15%) and cannabis (14%) were present in a minority of deaths in Turkey.

*Conclusions:* Deaths related to 3,4 methylenedioxymethamphetamine (MDMA) increased in Australia, Finland, Portugal and Turkey between 2011 and 2017. MDMA toxicity alone can be fatal but multiple drug toxicity remains more prevalent.

## Introduction

An estimated 21 million people worldwide reported the use of 3,4 methylenedioxymethamphetamine (MDMA) in the past 12 months (1). Patterns of MDMA consumption across most countries appear to be infrequent (1-5), and there is limited evidence for the existence of an MDMA dependence syndrome (6-8). Literature also suggests that harms arising from MDMA consumption are predominantly associated with acute adverse events (e.g. jaw clenching, increased heart rate, dizziness and hyperactivity) (9) that are relatively modest and transient in their impact (10). Some of the more serious adverse effects however, include tachycardia, hypertension, hyperthermia, serotonin syndrome, seizures, stroke, hyponatremia and cardiac arrest (9, 11, 12) as well as an elevated risk for traumatic injury and suicide (13). These risks can occur as a result of pharmacokinetic actions of MDMA as well as in response to environmental conditions (14), and in some instances can result in death (11, 15).

International MDMA markets have undergone substantial changes in more recent times, most notably with indications of increasing manufacture of high purity MDMA (16). Increased purity has important implications for MDMA use and harms, as research shows that use of MDMA where the dose exceeds 120 mg increases the risk of adverse effects (17). In Europe, the average MDMA content of tablets among countries routinely reporting data has been rising since 2010 and reached a 10-year high in 2018 (half the countries reported an average between 132 and 181 mg per tablet) (16) with some MDMA tablets recorded with doses exceeding 300mg (18).

Little is known about MDMA-related mortality internationally. Previous work in Australia has examined trends over time in MDMA-related deaths and circumstances under which these deaths occurred (13, 15).

Against a global context of high and increasing purity, and increased availability, and prevalence of MDMA use, this study extends previous work, updating Australian data, and reporting for the first time, trends in MDMA-related deaths in Finland, Portugal and Turkey.

**Aims**

This analysis aims to identify trends in MDMA-related mortality rates, and explores causes of death and median MDMA blood concentrations across countries.

**Methods**

***Seizures and Use***

Data are briefly presented on these indicators to provide some background on MDMA availability and use in each country. Data on the weight in kilograms of total MDMA seizures detected from the UNODC World Drug Report are reported (1). Data are reported on past year MDMA use among young adults (the group where use is highest) aged 25 to 34 years from the latest population survey available in each country (4, 5).

**Deaths**

Data for deaths in Australia were extracted (by author AR) from the National Coronial Information System (NCIS), an online database that contains information on all deaths reportable to a coroner. Data for deaths in Finland, Portugal, and Turkey were extracted (by authors PK, MJ & AC, and BS respectively) from the forensic toxicology databases available in each country, which are used for annual reporting to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (5, 19, 20).

*Case selection*

Two categories of deaths were included in the study; 1) Deaths where MDMA toxicity was considered by the forensic pathologist to be the *underlying* cause of death (with or without other drug toxicity), herein referred to as 'drug toxicity deaths'; and 2) Deaths where MDMA toxicity or intoxication were considered to be a *contributory* cause, herein referred to as 'other cause deaths'. This analysis refers to all deaths, drug toxicity and other cause deaths, as 'MDMA-related deaths.' Homicides were excluded in addition to deaths where MDMA was detected in toxicology but not attributed as causal or contributory to the death. Inclusion and exclusion criteria were applied consistently across all four countries.

*Toxicology*

Toxicology data were utilised to present other substances detected post-mortem by country. Median blood concentrations of MDMA in mg/L are presented where blood samples and quantitative results were available.

*Measures*

Demographic variables assessed included age at death and gender. Year of death was also extracted for inclusion in analysis. The cause of death variable (drug toxicity or other cause) was derived from the medical cause of death field as determined by the pathologist. Within the drug toxicity deaths, the variables multiple drug toxicity and MDMA toxicity alone were also derived from the medical cause of death field. Variables for the other drugs detected in toxicology were derived from the medical cause of death field and toxicology reports containing quantitative data on blood concentrations of drugs detected during coronial investigations. Median blood concentrations were calculated from quantitative data on blood concentrations contained in toxicology reports.

*Statistical Analyses*

This analysis has not been pre-registered on a public platform. Differences in age and gender by cause of death were assessed using logistic regression. Odds ratios (OR), 95% confidence intervals (95% CI) and p values were reported for these tests. Differences in median MDMA blood concentrations by cause of death were assessed using the Mann–Whitney U test.

The timeframe of data presented varies by country depending on data availability; 2001 to 2019 for Australia; 2001 to 2017 for Finland; 2008 to 2019 for Portugal; and 2009 to 2017 for Turkey.

Age-adjusted MDMA death rates per 100,000 population aged 15-64 were calculated for each country using estimates of the resident population in June each year for Australia (21), and in January of each year for Finland, Portugal and Turkey (22). Standardised mortality rates were then calculated for each country utilising World Health Organization (WHO) age-standardised world population figures – estimated average 2000-2025 (23). Standardised mortality rates allowed for comparisons over time across countries. Rates and trends across countries are placed in the context of MDMA market indicators (seizures detected and prevalence of use) in each country.

Standardised mortality rates were modelled using negative binomial regression where there was over-dispersion, and Poisson regression where there was not (24). Year was entered as a categorical variable into the regression, modelling all MDMA-related deaths for each country. Linear trends were statistically analysed for the period 2011–2017. Analyses for trends in rates of deaths were conducted using SAS 9.4 (25). All other analyses were performed in SPSS 26.0 (26).

The sequential Bonferroni method (27), applying an iterative stepwise adjustment of alpha values within each set of analyses by country, was used to account for multiple comparisons.

**Results**

***MDMA seizures and prevalence across countries***

Australia ranked in the top three countries internationally for the greatest quantity of MDMA seizures detected between 2014 and 2017, ranking first in three of these four years (with 4,374 kgs seized in 2014, 4,865 kgs in 2016, and 3,065 kgs in 2017) (Supplementary Figure 1) (1). Turkey ranked in the top three countries in three out of four years between 2014 and 2017, with weights ranging from 975 kgs to 2,332 kgs. Numbers of seizures have increased substantially in Australia and Turkey since 2011. Quantities of MDMA seized in Finland and Portugal have remained comparatively low, ranging from 2 to 41 kgs during this period. The number of seizures in Finland has fluctuated over time while numbers have increased in Portugal to 282 in 2017 (Supplementary Figure 1).

The prevalence of past-year MDMA use among Australians aged 25 to 34 years is highest (6% in 2019) (4) across the four countries, and internationally (1), followed by Finland (2.6% in 2018), Turkey (0.2% in 2017) and Portugal (0.1% in 2016) (5) (Supplementary Figure 2).

***Trends in standardised mortality rates over time***

The number of reported MDMA-related deaths were highest in Turkey (1,400 total deaths), followed by Australia (507 deaths), Finland (100 deaths) and Portugal (45 deaths). Rates of MDMA-related deaths increased significantly between 2011 and 2017 in; Australia (from 0.02 to 0.12 per 100,000) by an average of approximately 34% (95% CI: 14.2, 57.7) each year ($p<0.01$); Finland (from 0.09 to 0.33 per 100,00) by an average of approximately 21% (95% CI: 7.3, 37.4) each year ($p<0.05$); Portugal (from 0.03 to 0.12 per 100,000) by an average of approximately 36% (95% CI: 8.6, 70.9) each year ($p=0.01$); and Turkey (from 0.05 to 0.37 per 100,000) by an average of approximately 44% (95% CI: 24.9, 67.2) each year ($p <0.0001$) (Figure 1). In 2017, rates were highest in Turkey (0.37 per 100,000 population), followed by Finland (0.33 per 100,000), Australia (0.12 per 100,000) and Portugal (0.12 per 100,000).

**Insert Figure 1 here**

*Demographic characteristics*

Deaths occurred predominantly among males across all four countries (ranging from 81% in Australia to 94.8% in Portugal) (Table 1). The median age of decedents ranged from 24 years in Finland to 27.5 years in Portugal. There were no differences in age between males and females in Turkey or Finland, while in Australia, females were significantly younger than males (24 v 27 years, U=23,242.0, p<0.01) (Figure 2). Small numbers of female decedents in Portugal precluded gender analysis.

**Insert Figure 2 here**

*Cause of death*

The majority of MDMA-related deaths in each country (except Portugal – 44%) were attributed to drug toxicity (from 60-70%), with smaller proportions attributed to other causes (from 30 to 40%) (Table 1). A total of 813 (40%) out of 2,052 deaths were attributed to causes other than drug toxicity across the four countries, accounting for 39% of deaths in Australia, 30% in Finland, 40% in Turkey, and 56% in Portugal (Table 1). These deaths were due to traumatic (mostly motor vehicle) accidents, with smaller proportions attributed to suicide and disease (data not shown).

Age differences were apparent by cause of death however, this varied across countries. In Turkey, decedents of drug toxicity deaths were significantly younger than those of other cause deaths (26 vs 28 years, U=183645.0, p=0.01). Decedents of drug toxicity deaths in Australia (27 vs 25 years, U=34,644.0, p=0.01) were significantly older than those of other cause deaths. No age differences were found between the causes of death in Finland or Portugal (Table 1).

Decedents of MDMA toxicity alone deaths were significantly younger than those of multiple drug toxicity deaths in Australia (24 vs 28 years, U=10,116.5, p=0.000) and Turkey (24 vs 27 years, U85967.0, p=0.000). No age differences were found among these deaths in Finland, and small numbers in Portugal precluded testing (Table 1).

Gender differences were apparent concerning the cause of death in Australia, with fatalities among females significantly more likely to be attributed to drug toxicity than among males (OR 1.2, 95% CI 1.1-1.4, p=0.018) (Table 1). Specifically, women were significantly more likely to die as a result of MDMA toxicity alone than men in Australia (OR 2.8, 95% CI 1.8-4.3, p=0.000) (Table 1). No gender differences were apparent by cause of death in Turkey or Finland, and small numbers in Portugal precluded further analysis.

In Australia, where deaths were attributed to drug toxicity, females were significantly younger than males (23 vs 28 years, U=10,474.0, p=0.000). No gender differences in age were found across the remaining countries (Table 1).

**Insert Table 1 here**

***Toxicology***

MDMA was detected in all deaths. Quantitative data on MDMA blood concentrations were available in 435 (86%) deaths in Australia, 81 (81%) deaths in Finland, 44 (98%) deaths in Portugal, and 271 (19%) deaths in Turkey. Overall, drug toxicity deaths had significantly higher blood MDMA concentrations than other cause deaths in Australia (U=27382.5, p=0.000) and Turkey (U=12579.5, p=0.000). No overall differences were found in Portugal or Finland (Figure 3.1). Among drug toxicity deaths (N=1,239), those attributable to MDMA toxicity alone (N=441; 36%) had a significantly higher blood MDMA concentration than multiple drug toxicity deaths in Australia (U=3045.5, p=0.000), Finland (U=133.0, p=0.002),

and Turkey (U=2148.0, p=0.000), with no differences found between these concentrations in Portugal (Figure 3.2). Complete data on the ranges of MDMA blood concentrations on cases where available are presented in Supplementary Tables 1A through 1D.

**Insert Figure 3 here**

Other substances were commonly detected in addition to MDMA in post-mortem toxicology. Psychostimulants were the most prevalent substance seen across most countries, as well as alcohol and cannabis. There were differences across countries concerning the specific substances identified, with cannabis and synthetic cannabinoids commonly detected in Turkey, and high proportions of deaths with opioids and benzodiazepines detected in Finland. Alcohol was detected in almost half of the cases in Portugal (49%), Australia (46%) and one-third in Finland (36%). Small numbers of deaths in Australia and Finland had new psychoactive substances (NPS) present, including paramethoxyamphetamine, alpha-PVP, and methcathinone. Apart from synthetic cannabinoids, NPS were not detected among MDMA-related deaths in Portugal or Turkey (Table 2).

**Insert Table 2 here**

## Discussion

To the best of our knowledge, this paper represents the first international cross-country analysis of MDMA-related mortality. Despite documented national differences in MDMA availability (seizures) and prevalence (surveys) of use, trends in deaths from 2011 to 2017 showed a similar pattern across the four countries (Australia, Finland, Portugal and Turkey), with rates of deaths increasing during this time. The decedents across all countries were predominantly young males in their mid-twenties and this is consistent with the data presented on the prevalence of past-year MDMA use in each country.

Deaths across three of the countries (Australia, Finland and Turkey) were mainly due to acute (mostly multiple) drug toxicity, with minorities (13% to 25%) of all deaths attributed solely to MDMA toxicity. These findings are consistent with drug-related mortality in general, showing that most deaths occur in the context of concomitant or polydrug use (28, 29).

Similarities across countries were apparent in relation to age and gender by cause of death, however, some of these were difficult to detect due to small numbers. Decedents of drug toxicity deaths in Australia were significantly older than those of other cause deaths. This relationship was also apparent in Portugal, but small numbers meant the finding did not reach significance. Older age among toxicity deaths most likely reflects the over-representation of young men in motor vehicle (the majority of other cause) deaths (30). Interestingly, the reverse was true in Turkey, with decedents of drug toxicity deaths significantly younger than those of other cause deaths. These age differences in Turkey are consistent with a reportedly younger population of drug consumers, and younger age of those who die from a drug overdose compared to the European average (5, 16). Concerning gender, deaths among females in Australia were significantly more likely to be attributed to drug toxicity than other causes. This relationship was also apparent in Finland, but small numbers meant the finding did not reach significance. Australian women were significantly more likely to die from MDMA toxicity

alone. These findings may reflect gender differences in MDMA toxicity, with some research suggesting women are likely to be at greater risk of toxicity than men (31).

Toxicology findings provided important insights into these deaths. MDMA blood concentrations were significantly higher among drug toxicity than other cause deaths in Australia and Turkey. Specifically, concentrations were significantly higher among MDMA toxicity alone than multiple drug toxicity deaths across three (Australia, Finland and Turkey) of the four countries. Interestingly the range of blood concentrations was broad, with some fatalities occurring in the context of very low concentrations. Previous literature documents that MDMA toxicity fatalities have primarily occurred with MDMA blood concentrations greater than 0.5mg/L (32). The majority of deaths (where quantitative data were available) across all four countries in the current study were linked with concentrations above 0.5mg/L. However, blood concentration is only one of a multitude of factors involved in MDMA fatalities (33), with other mechanisms of death also likely, accounting for the large ranges in blood concentrations that are seen among these deaths (32). In addition, variations in time to death can also influence post-mortem redistribution of MDMA and median blood concentrations (34). Further research on the mechanisms involved in MDMA-related deaths is required.

Other drugs implicated in these deaths varied by country, although other stimulants, alcohol and cannabis were common across all four countries. Synthetic cannabinoids featured in substantial minorities of MDMA deaths in Turkey, while benzodiazepines and opioids were prevalent in Finland. Consistent with these findings, two-thirds of all drug-induced deaths in Turkey in 2017 involved synthetic cannabinoids (19).

Placing these findings in the context of demographics and market indicators (seizures and use) presented, it is unsurprising that the absolute number of deaths in Turkey and Australia were the highest among the four countries (also noting much larger population sizes - 79 and 25

million respectively - than Portugal and Finland – 10 and 5 million) (21, 22). In 2017, Australia recorded the highest seizure weight, the highest prevalence of MDMA use globally (35), and a much higher prevalence of use compared to the other three countries studied. Turkey recorded the second-highest seizure weight globally in 2017, and more MDMA is now seized in Turkey than in the European Union as a whole (29). Turkey is located within one of the key drug trafficking routes connecting Europe and Asia (16, 36). While it has traditionally been seen as a transit country, there is now growing evidence to suggest that illicit drug use within Turkey is increasing (36). Despite the low population prevalence of MDMA use reported in Turkey, other data such as treatment presentations, seem to indicate MDMA use is on the rise (16).

Rates of MDMA-related deaths in Finland were also comparatively high, and the prevalence of MDMA use higher than in the other two European countries considered in this paper. In 2018, Finland recorded the third-highest past-year prevalence of MDMA use among young adults aged 25-34 years across Europe, behind the Netherlands and Belgium (5). Interestingly, seizure data showed low numbers and weights of seizures which may reflect Finland's close geographic proximity to the MDMA manufacturing countries - the Netherlands and Belgium (1). Wastewater analysis shows that MDMA use has steadily increased in Finland between 2012 and 2019 (37, 38).

Deaths in Portugal, although increasing, were occurring at a much lower rate, and in the context of the relatively low prevalence of use and small numbers/weights of MDMA seizures detected. Analysis of wastewater data in Portugal also suggests MDMA use has increased between 2015 and 2019 (38).

Our findings have important public health implications. This paper shows that MDMA toxicity, in the absence of other substances, can be fatal. The fatal nature of MDMA toxicity alone is an important message for consumers, particularly within the context of high purity MDMA which is readily available in both Australia and across Europe (35). A recent coronial inquest into

MDMA-related deaths occurring at festivals in Australia found that young consumers were unaware of MDMA market changes (increasing purity) and the potential risks of fatal toxicity (33), highlighting the urgent need for messages targeting these groups. The dangers of concomitant drug use also need to be emphasised. The use of multiple (MDMA and other) stimulants places more significant stress on the cardiovascular system, increasing the probability of toxicity. The presence of alcohol among these deaths is important. Alcohol use at high levels has been shown to exacerbate cardiotoxic effects (39), and in combination with MDMA synergistically increases blood concentrations of both substances, potentiating toxicity (40). The presence of synthetic cannabinoids among deaths in Turkey also has public health implications. The pharmacologic effects of synthetic cannabinoids most closely resemble those of stimulants and primarily include cardiotoxic effects (41), which may increase the toxicity of both substances when used in combination. While there is less known about the interaction between MDMA and central nervous system depressants such as benzodiazepines and opioids (42), some opioids have implications for potentiating serotonin toxicity (43), as does MDMA (42). Warning consumers of the *specific risks* associated with combining particular substances with MDMA is critical in reducing MDMA-related harms. Finally, this study highlights the importance of toxicology data in informing the determination of the cause of death, as well as providing necessary surveillance on the changing risks and nature of MDMA-related deaths internationally. These data are central to drug-related death investigations as they provide essential contextual information.

*Strengths and Limitations*

The strengths of this study are the use of data extracted from coronial and forensic databases across the countries. This enables collection of details from the results of coronial investigative procedures, allowing for differentiation of MDMA from amphetamine-related deaths. This distinction is not possible in general mortality registries that use the International Classification

of Diseases (ICD-10) coding structure (44). The 2021 edition of ICD-10 coding (effective October 2020) (45) now includes a code specifically for MDMA poisoning however coronial and forensic data are likely to remain the most sensitive method for monitoring MDMA-related mortality until the updated coding structure is fully implemented. Coronial and forensic data also allow for more detailed analyses of the circumstances of death compared to data from general mortality registers. Limitations also warrant discussion. Firstly, given the complexity of coronial investigations, we may not have captured all MDMA-related deaths during the period as some investigations may not be complete. Second, there are likely to be differences within and across countries in the types of routinely tested drugs in drug-related death investigations. This may lead to an underestimate in numbers and rates of MDMA-related deaths. Finally, quantitative data on MDMA blood concentrations was not available in all cases, which may have biased these findings. This was particularly true for Turkey. However, comparative analysis of Turkish cases with and without blood concentration data showed no differences in demographic characteristics (gender or age).

**Conclusion**

This study provides new insights into MDMA-related deaths across several countries in Europe, and comparisons with Australia. Findings show that most deaths occur among males, and that deaths are premature, given the decedents were aged in their mid-twenties. MDMA toxicity alone can be fatal. Nonetheless multiple drug toxicity remains most prevalent overall in MDMA-related deaths. Similarities across countries were evident; increasing trends were seen in all four countries, and similar trends were seen in toxicology findings, with higher MDMA blood concentrations associated with deaths due to MDMA toxicity alone. Differences across countries were also apparent, particularly concerning other drugs detected in toxicology. This highlights the need for targeted harm reduction messages in the context of local patterns of illicit drug use. Warning young consumers about the risks associated with MDMA use, alone

and in combination with other drugs, is critical, particularly in the context of rapidly changing drug markets globally.

**Acknowledgements**

The authors gratefully acknowledge the support of the Victorian Operational Infrastructure Fund. We would also like to acknowledge; the Victorian Department of Justice and Community Safety for providing access to the National Coronial Information System in Australia; The authors are grateful to the Reitox network of national focal points and technical experts working in Europe for providing data, and colleagues at the EMCDDA for compiling and analysing data collected as part of the EMCDDA ongoing monitoring of the drug situation.

## References


1. UNITED NATIONS OFFICE ON DRUGS AND CRIME. World Drug Report 2020, Geneva: United Nations Office on Drugs and Crime; 2020.
2. PEACOCK A., KARLSSON A., UPOROVA J., GIBBS D., SWANTON R., KELLY G. et al. Australian Drug Trends 2019: Key findings from the Ecstasy and Related Drugs Reporting System (EDRS), Sydney, UNSW: National Drug and Alcohol Research Centre, UNSW; 2019.
3. SUBSTANCE ABUSE AND MENTAL HEALTH SERVICES ADMINISTRATION. Key substance use and mental health indicators in the United States: Results from the 2018 National Survey on Drug Use and Health, Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration; 2019.
4. AUSTRALIAN INSTITUTE OF HEALTH AND WELFARE. National Drug Strategy Household Survey 2019, Canberra: Australian Institute of Health and Welfare; 2020.
5. EUROPEAN MONITORING CENTRE FOR DRUGS AND DRUG ADDICTION. EMCDDA Statistical Bulletin 2020, Lisbon: EMCDDA; 2020.
6. DEGENHARDT L., BRUNO R., TOPP L. Is ecstasy a drug of dependence?, Drug Alcohol Depend 2010: 107: 1-10.
7. MITHOEFER M. C., WAGNER M. T., MITHOEFER A. T., JEROME L., MARTIN S. F., YAZAR-KLOSINSKI B. et al. Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3,4-methylenedioxymethamphetamine-assisted psychotherapy: a prospective long-term follow-up study, J Psychopharmacol 2013: 27: 28-39.
8. SCHENK S., HELY L., GITTINGS D., LAKE B., DANIELA E. Effects of priming injections of MDMA and cocaine on reinstatement of MDMA- and cocaine-seeking in rats, Drug and Alcohol Dependence 2008: 96: 249-255.
9. PARROTT A. C. Human psychobiology of MDMA or 'Ecstasy': an overview of 25 years of empirical research, Hum Psychopharmacol 2013: 28: 289-307.
10. VIZELI P., LIECHTI M. E. Safety pharmacology of acute MDMA administration in healthy subjects, J Psychopharmacol 2017: 31: 576-588.
11. SCHIFANO F. A bitter pill. Overview of ecstasy (MDMA, MDA) related fatalities, Psychopharmacology (Berl) 2004: 173: 242-248.
12. NOSEDA R., SCHMID Y., SCHOLZ I., LIAKONI E., LIECHTI M. E., DARGAN P. I. et al. MDMA-related presentations to the emergency departments of the European Drug Emergencies Network plus (Euro-DEN Plus) over the four-year period 2014-2017, Clin Toxicol (Phila) 2020: 1-7.
13. KAYE S., DARKE S., DUFLOU J. Methylenedioxymethamphetamine (MDMA)-related fatalities in Australia: Demographics, circumstances, toxicology and major organ pathology, Drug and Alcohol Dependence 2009: 104: 254-261.
14. GREEN A. R., O'SHEA E., COLADO M. I. A review of the mechanisms involved in the acute MDMA (ecstasy)-induced hyperthermic response, Eur J Pharmacol 2004: 500: 3-13.
15. ROXBURGH A., LAPPIN J. MDMA-related deaths in Australia 2000 to 2018, Int J Drug Policy 2020: 76: 102630.
16. EUROPEAN MONITORING CENTRE FOR DRUGS AND DRUG ADDICTION AND EUROPOL. EU Drug Markets Report 2020, Luxembourg: Publications Office of the European Union; 2020.

17. BRUNT T. M., KOETER M. W., NIESINK R. J., VAN DEN BRINK W. Linking the pharmacological content of ecstasy tablets to the subjective experiences of drug users, Psychopharmacology (Berl) 2012: 220: 751-762.
18. EUROPEAN MONITORING CENTRE FOR DRUGS AND DRUG ADDICTION. Recent changes in Europe's MDMA/ecstasy market. Results from and EMCDDA Trendspotter study, Lisbon, Portugal: European Monitoring Centre for Drugs and Drug Addiction; 2016.
19. EUROPEAN MONITORING CENTRE FOR DRUGS AND DRUG ADDICTION. Turkey, Country Drug Report 2019, Lisbon: EMCDDA; 2019.
20. HAUKKA J., KRIIKKU P., MARIOTTINI C., PARTONEN T., OJANPERÄ I. Non-medical use of psychoactive prescription drugs is associated with fatal poisoning, Addiction 2018: 113: 464-472.
21. AUSTRALIAN BUREAU OF STATISTICS. Estimated Resident Population by Single Year of Age, Australia; 2019.
22. EUROPEAN COMMISSION. Population statistics in Europe by country by year: Eurostats; 2019.
23. AHMAD O., BOSCHI-PINTO C., LOPEZ A., MURRAY C., LOZANO R., INOUE M. Age standardisation of rates: A new WHO standard, Geneva: World Health Organization; 2001.
24. COXE S., WEST S. G., AIKEN L. S. The analysis of count data: a gentle introduction to Poisson regression and its alternatives, J Pers Assess 2009: 91: 121-136.
25. SAS INSTITUTE INC. SAS® 9.4 Cary, NC: SAS Institute 2015.
26. SPSS INC. PASW Statistics 25.0, Chicago: SPSS Inc; 2017.
27. HOLM S. A simple sequentially rejective multiple test procedure., Scand J Stat 1979: 6: 65-70.
28. ROXBURGH A., DOBBINS T., DEGENHARDT L., PEACOCK A. Opioid-, amphetamine-, and cocaine-induced deaths in Australia: August 2018 Sydney: National Drug and Alcohol Research Centre, UNSW Sydney; 2018.
29. EUROPEAN MONITORING CENTRE FOR DRUGS AND DRUG ADDICTION. European Drug Report 2019: Trends and Developments Luxembourg: Publications Office of the European Union; 2019.
30. SEHGAL A. R. Lifetime Risk of Death From Firearm Injuries, Drug Overdoses, and Motor Vehicle Accidents in the United States, Am J Med 2020.
31. ALLOTT K., REDMAN J. Are there sex differences associated with the effects of ecstasy/3,4-methylenedioxymethamphetamine (MDMA)?, Neurosci Biobehav Rev 2007: 31: 327-347.
32. KALANT H. The pharmacology and toxicology of "ecstasy" (MDMA) and related drugs, Cmaj 2001: 165: 917-928.
33. STATE CORONERS COURT OF NEW SOUTH WALES. Inquest into the death of six patrons of NSW music festivals. In: State Coroners Court of New South Wales, editor, Sydney, NSW; 2019.
34. APPLE F. S. Postmortem Redistribution of Drugs. In: Levine B.S. & Kerrigan S., editors. Principles of Forensic Toxicology, Switzerland: Springer, Cham; 2020, p. 595-601.
35. UNITED NATIONS OFFICE ON DRUGS AND CRIME. World Drug Report 2019, Geneva: United Nations Office on Drugs and Crime; 2019.
36. EVERED K. T., EVERED E. "Not just eliminating the mosquito but draining the swamp": A critical geopolitics of Turkish Monitoring Center for Drugs and Drug Addiction and Turkey's approach to illicit drugs, Int J Drug Policy 2016: 33: 6-14.

37. KANKAANPÄÄ A., ARINIEMI K., HEINONEN M., KUOPPASALMI K., GUNNAR T. Current trends in Finnish drug abuse: Wastewater based epidemiology combined with other national indicators, Sci Total Environ 2016: 568: 864-874.
38. EUROPEAN MONITORING CENTRE FOR DRUGS AND DRUG ADDICTION. Wastewater analysis and drugs — a European multi-city study, Lisbon, Portugal; 2020.
39. WALKER R. K., COUSINS V. M., UMOH N. A., JEFFRESS M. A., TAGHIPOUR D., AL-RUBAIEE M. et al. The good, the bad, and the ugly with alcohol use and abuse on the heart, Alcohol Clin Exp Res 2013: 37: 1253-1260.
40. LIANG M., ZHANG J., ZHENG N., LIU L. How Postmortem Redistribution of MDMA in Acute Alcohol-MDMA Combined-Use Rats Change under Effects of Alcohol, Sci Rep 2017: 7: 4038.
41. COOPER Z. D. Adverse Effects of Synthetic Cannabinoids: Management of Acute Toxicity and Withdrawal, Curr Psychiatry Rep 2016: 18: 52.
42. SCHIFANO F. A bitter pill. Overview of ecstasy (MDMA,MDA) related fatalities, Psychopharmacology 2004: 242-248.
43. SCHENK M., WIRZ S. [Serotonin syndrome and pain medication : What is relevant for practice?], Schmerz 2015: 29: 229-251.
44. WORLD HEALTH ORGANIZATION. The International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), Geneva: World Health Organization; 2010.
45. ICD10DATA.COM. 2021 ICD-10-CM Diagnosis Code T43.64, Poisoning by ecstasy; 2021.

**Figure 1: Standardised mortality rates of MDMA-related deaths per 100,000 population aged 15-64, by country and cause of death**

**Figure 1.1 Australia, 2001-2017**

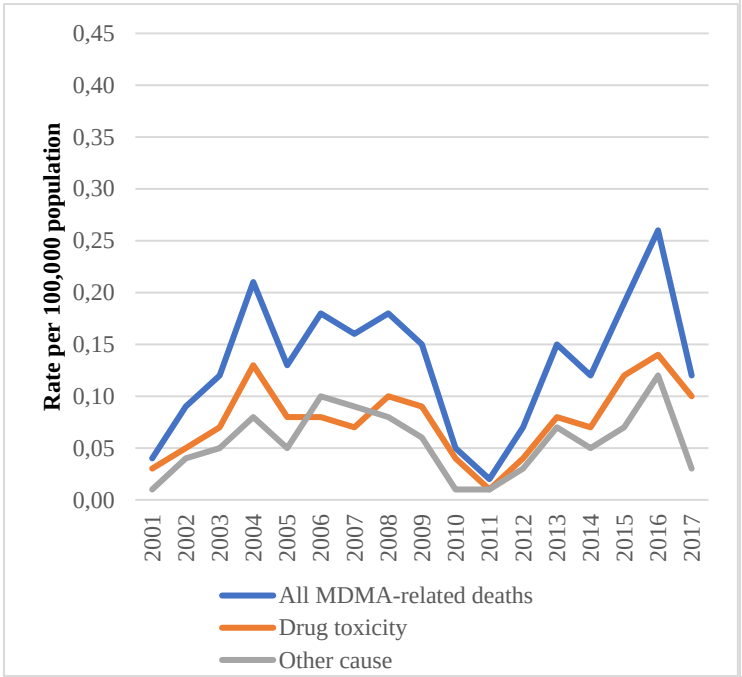
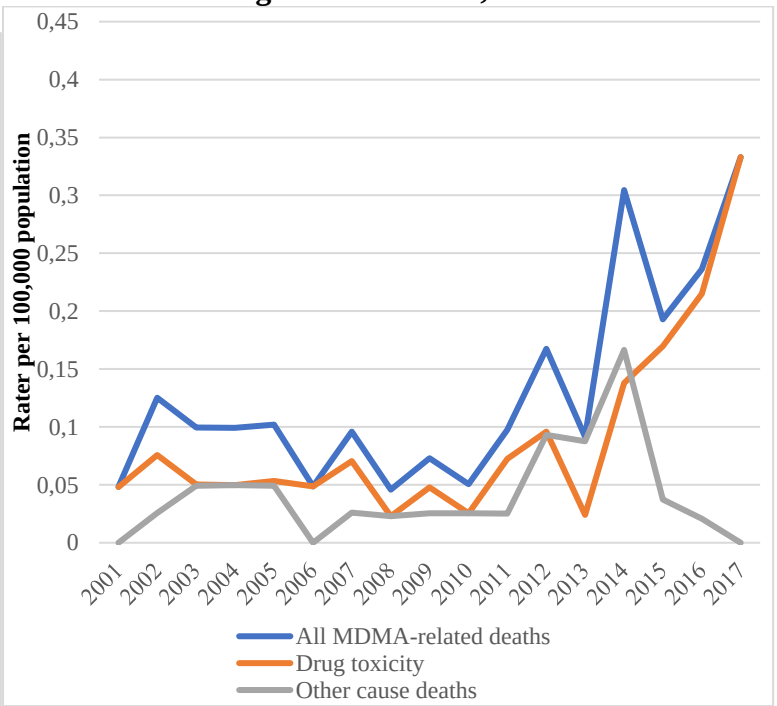



**Figure 1.2 Finland, 2001-2017**




**NB:** Statistical analysis conducted on trends across countries between 2011 and 2017.

**Figure 1.3 Portugal, 2009-2017**

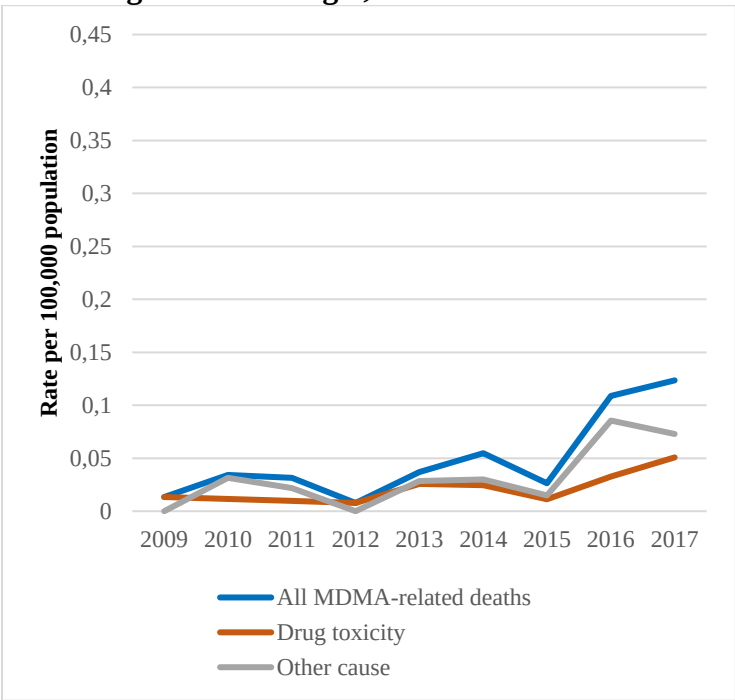
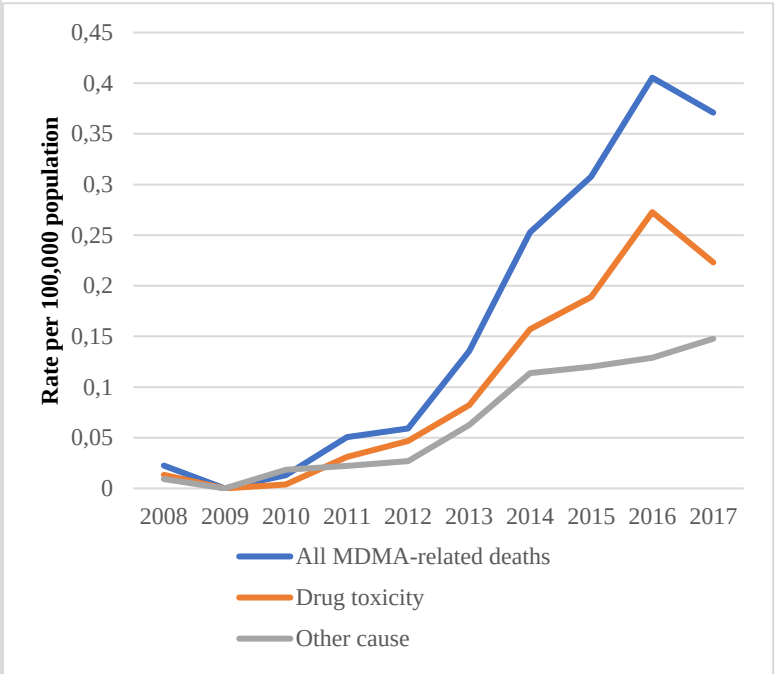
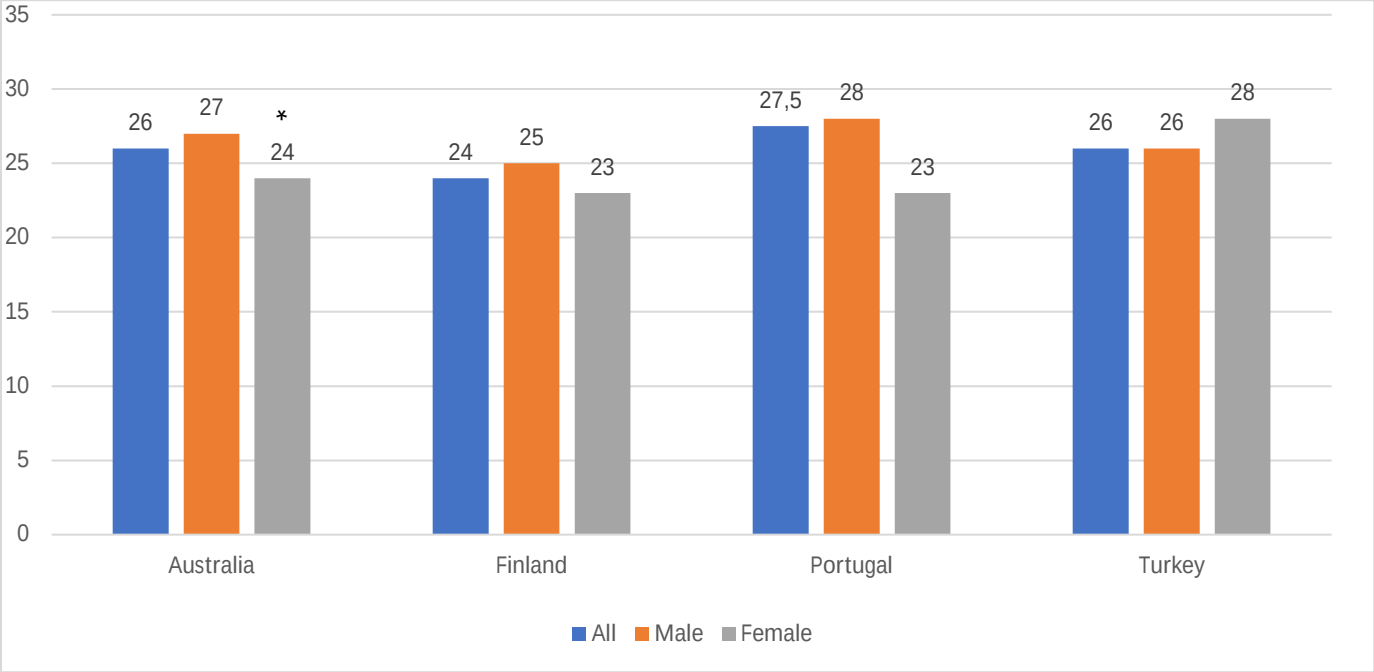



**Figure 1.4 Turkey, 2008-2017**




**NB:** Statistical analysis conducted on trends across countries between 2011 and 2017.

**Figure 2: Deaths by median age, gender and country**




*Statistically significant difference

**Table 1: Cause of MDMA-related deaths by gender and country**

| **Australia** | **Total (N=507)** | | **Female (N=95)** | | **Male (N=412)** | |
|---|---|---|---|---|---|---|
| | n (%) | Median age (range) | n (%) | Median age (range) | n (%) | Median age (range) |
| ***Drug toxicity (all)*** | ***309 (61)*** | 27 (15-60) [a] | ***68 (72)*** [c] | 23 (15-54) [d] | ***241 (58)*** | 28 (17-60) |
| Multiple drug toxicity | 241 (48) | 28 (15 to 58) | 41 (43) | 26 (17-54) | 200 (48) | 28.5 (17-58) |
| MDMA toxicity only | 68 (13) | 24 (15-60) [b] | 27 (29) | 21 (15-37) | 41 (10) | 26 (17-60) |
| ***Other cause*** | ***198 (39)*** | 25 (16 -58) | ***27 (28)*** | 25 (17-40) | ***171 (42)*** | 25 (16-58) |
| **Finland** | **Total (N=100)** | | **Female (N=19)** | | **Male (N=81)** | |
| | n (%) | Median age (range) | n (%) | Median age (range) | n (%) | Median age (range) |
| ***Drug toxicity (all)*** | ***70 (70)*** | 24.5 (17-53) | ***18 (95)*** | 23 (19-44) | ***52 (65)*** | 25 (17-53) |
| Multiple drug toxicity | 57 (57) | 25 (17-53) | 15 (79) | 24 (19-44) | 42 (52) | 25 (17-53) |
| MDMA toxicity only | 13 (13) | 22 (18-38) | <5 (16) | N/A | 10 (13) | 23.5 (18-38) |
| ***Other cause*** | ***30 (30)*** | 23.5 (17- 47) | ***<5 (5)*** | N/A | ***29 (35)*** | 24 (17-47) |
| **Portugal** | **Total (N=45)** | | **Female (N=3)** | | **Male (N=42)** | |
| | n (%) | Median age (range) | n (%) | Median age (range) | n (%) | Median age (range) |
| ***Drug toxicity (all)*** | ***20 (44)*** | 32 (18-47) | ***3 (100)*** | 23 (20-32) | ***17 (41)*** | 34 (18-47) |
| Multiple drug toxicity | 13 (28) | 34 (20-42) | 2 (66) | N/A | 11 (27) | 34 (20-42) |
| MDMA toxicity only | 7 (16) | 32 (18-47) | 1 (34) | N/A | 6 (14) | 32 (18-47) |
| ***Other cause*** | ***25 (56)*** | 26 (16- 38) | ***0*** | N/A | ***25 (59)*** | 26 (16-38) |
| **Turkey** | **Total (N=1400)** | | **Female (N=86)** | | **Male (N=1314)** | |
| | n (%) | Median age (range) | n (%) | Median age (range) | n (%) | Median age (range) |
| ***Drug toxicity (all)*** | ***840 (60)*** | 26 (14-59) [a] | ***51 (60)*** | 25 (15-60) | ***789 (60)*** | 26 (14-59) |
| Multiple drug toxicity | 487 (35) | 27 (15-58) | 35 (30) | 25 (18-47) | 457 35) | 27 (15-58) |
| MDMA toxicity only | 353 (25) | 24 (15-58) [b] | 24 (21) | 24 (16-50) | 332 (25) | 24 (14-59) |
| ***Other cause*** | ***560 (40)*** | 28 (13-60) | ***35 (40)*** | 29 (16-43) | ***525 (40)*** | 27 (13-60) |

[a] Statistically significant difference in median age between drug toxicity and other cause deaths.

[b] Statistically significant difference in median age between MDMA toxicity and multiple drug toxicity deaths.

[c] Statistically significant difference in proportions of females and males.

[d] Statistically significant difference in median age of females and males

**Figure 3: Median blood concentrations (mg/L) of MDMA by cause of death and country**

**Figure 3.1: Drug toxicity vs Other cause deaths**

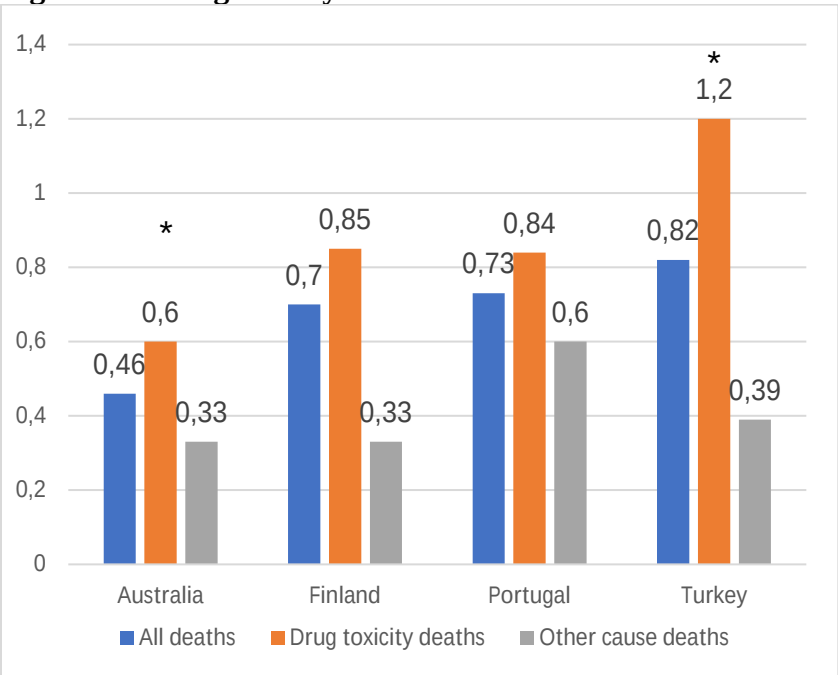



**Figure 3.2: Multiple drug vs MDMA alone toxicity**

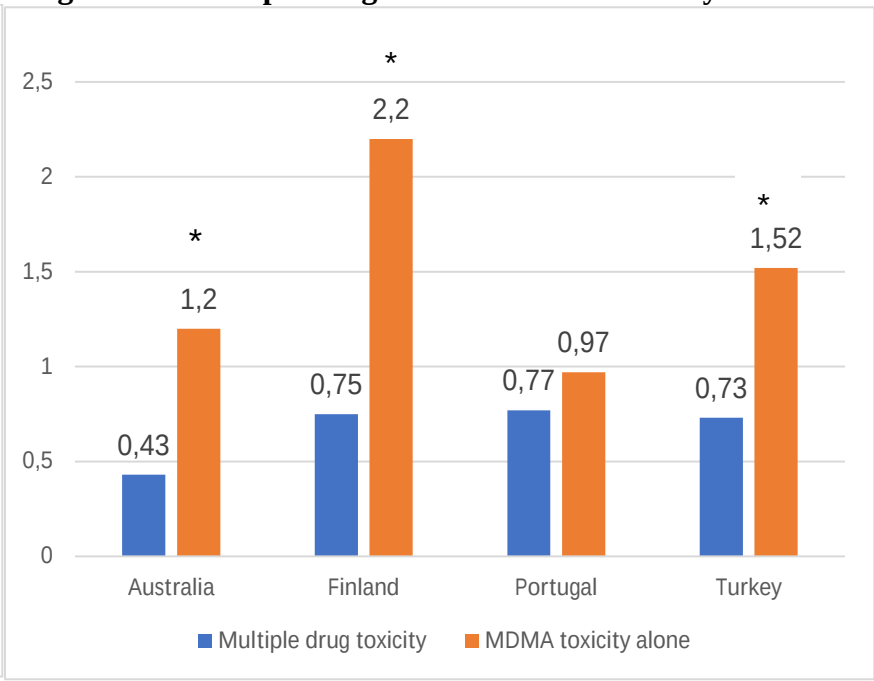


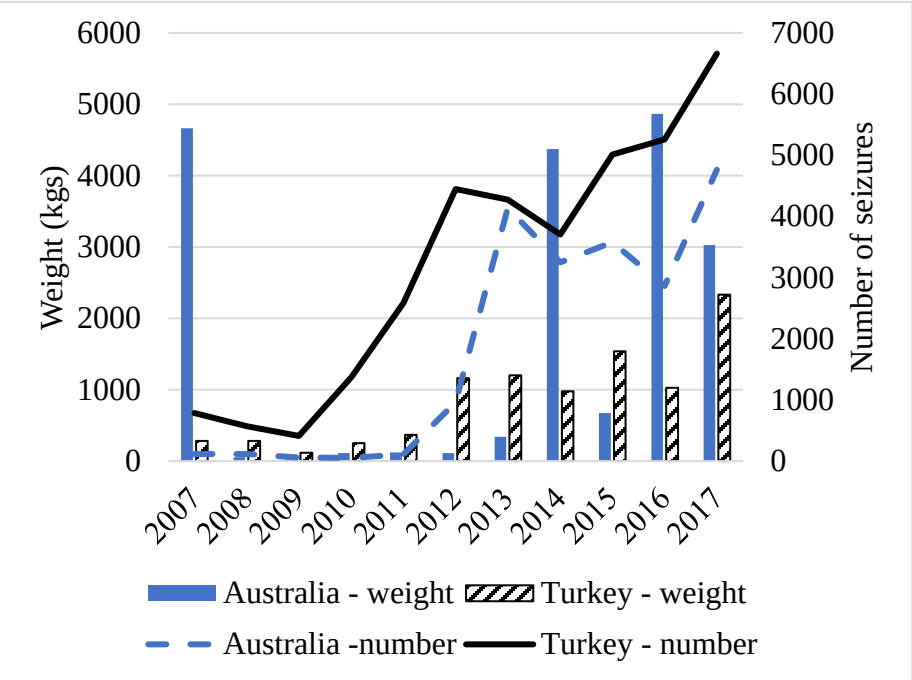
**Table 2: Presence of other drugs in toxicology of MDMA-related deaths by country**

| Drug | Australia N=435 n (%) | Finland N=83 n (%) | Portugal N=45 (n) (%) | Turkey n=1400 n (%) |
|---|---|---|---|---|
| ***Psychostimulants*** | 226 (52) | 51 (61) | 12 (27) | 218 (16) |
| Amphetamine | 0 | 45 (54) | 2 (4) | 94 (7) |
| Methamphetamine | 170 (39) | 7 (8) | 1 (2) | 127 (9) |
| Cocaine | 77 (18) | 7 (8) | 11 (24) | 122 (9) |
| Alcohol | 198 (46) | 30 (36) | 22 (49) | 225 (16) |
| Opioids | 122 (28) | 53 (64) | 5 (11) | 192 (14) |
| Cannabis | 110 (25) | 31 (37) | 21 (47) | 463 (33) |
| Benzodiazepines | 100 (23) | 67 (81) | 6 (13) | 75 (5) |
| Synthetic Cannabinoids | 0 | 0 | 0 | 208 (15) |
| Other NPS* | 26 (6) | 13 (16) | 0 | 0 |

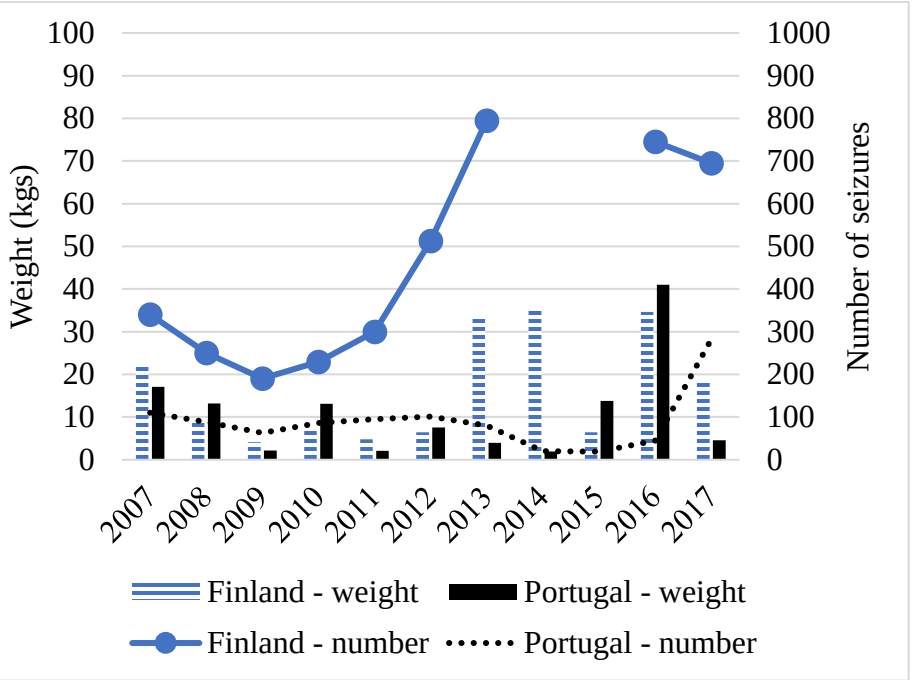
*Includes paramethoxyamphetamine, alpha-PVP, ephedrine, methylphenidate, methcathinone, MDPV, and MDEA.

**Supplementary Figure 1: Weight in kilograms and number of MDMA seizures by country**

**Supp. Figure 1.1: Number and weight of seizures, Australia and Turkey**

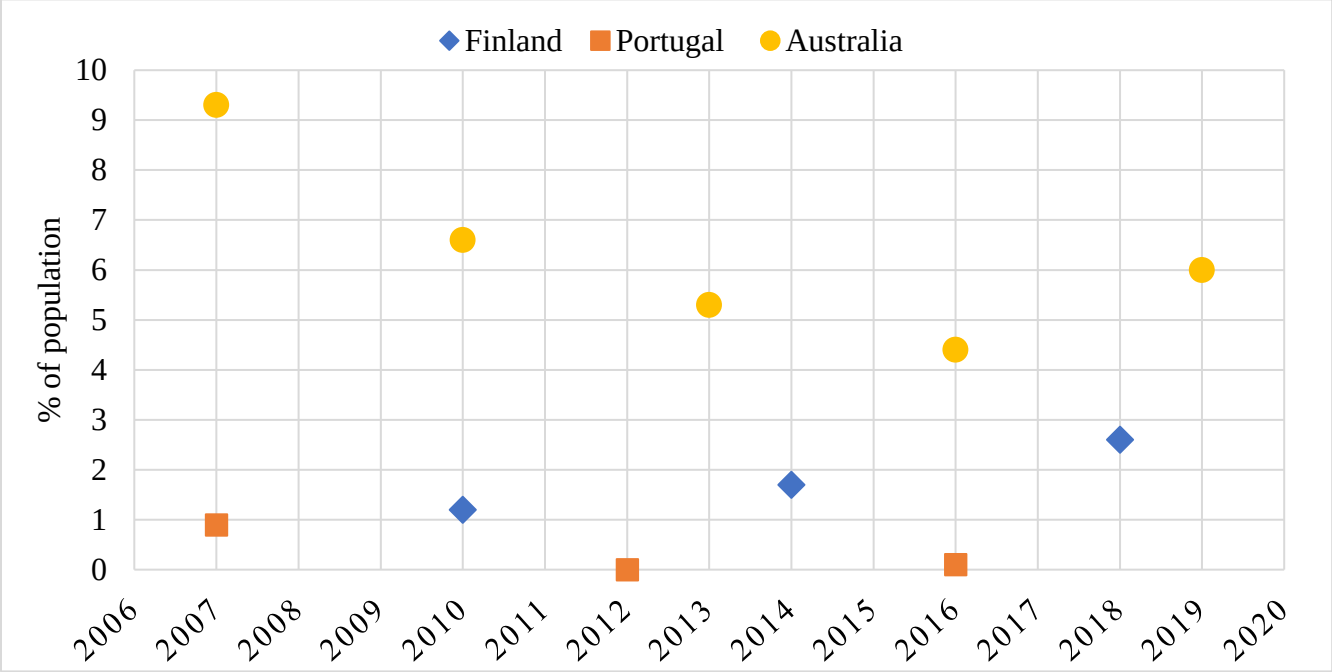



**Supp. Figure 1.2: Number and weight of seizures, Finland and Portugal**




**Sources:** Department of Home Affairs Australia; European Drug Report 2019; EMCDDA Statistical Bulletin 2019; UNODC World Drug Report 2020
**NB:** Data for the number of seizures in Finland were missing for the years 2014 and 2015.

**Supplementary Figure 2: Past year population prevalence of MDMA use among those aged 25 to 34 years, by country 2007-2020**




**NB:** Data for Turkey not shown as there was only one year available, and it is thought to be under representative of the true prevalence of MDMA use.
**Source:** AIHW, 2020; EMCDDA, 2020

**Supplementary Table 1A: Median blood concentrations of MDMA by cause of death and gender, Australia***

| | All deaths | | Males | | Females | |
|---|---|---|---|---|---|---|
| | **Median mg/L (range)** | **Numbers*** | **Median mg/L (range)** | **Numbers*** | **Median mg/L (range)** | **Numbers*** |
| *Drug toxicity* | 0.60 (0.01-64.00) | 262 | 0.52 (0.01-64.00) | 207 | 0.80 (0.02-22.00) | 55 |
| Multiple drug toxicity | 0.43(0.01-22.00) | 210 | 0.42 (0.01-14.00) | 176 | 0.64 (0.02-22.00) | 34 |
| MDMA toxicity | 1.20 (0.04-64.00) | 52 | 1.20 (0.07-64.00) | 31 | 1.10 (0.04-11.50) | 21 |
| *Other cause* | 0.33(0.01-8.40) | 173 | 0.30 (0.01-8.40) | 150 | 0.46 (0.01-6.80) | 23 |
| **All Deaths** | **0.46 (0.01-64.00)** | **435** | **0.42 (0.01-64.00)** | **357** | **0.66 (0.17-22.00)** | **78** |

* Where quantitative data available for femoral blood. Quantitative toxicology data on concentrations were available in 87% of cases (88% of males and 85% of females).

**Supplementary Table 1B: Median blood concentrations of MDMA by cause of death and gender, Finland***

| | All deaths | | Males | | Females | |
|---|---|---|---|---|---|---|
| | **Median mg/L (range)** | **Numbers*** | **Median mg/L (range)** | **Numbers*** | **Median mg/L (range)** | **Numbers*** |
| *Drug toxicity* | 0.85 (0.04-5.20) | 60 | 0.81 (0.07-5.20) | 45 | 1.00 (0.04-4.80) | 15 |
| Multiple drug toxicity | 0.72 (0.04-5.20) | 47 | 0.69 (0.07-5.20) | 35 | 0.94 (0.04-3.70) | 12 |
| MDMA toxicity | 2.20 (0.34-5.20) | 13 | 2.50 (0.34-5.20) | 10 | 2.10 (0.70-4.80) | 3 |
| *Other cause* | 0.33 (0.42-23.00) | 21 | 0.35 (0.04-23.00) | 20 | N/A | 1 |
| **All Deaths** | **0.70 (0.04-23.00)** | **81** | **0.65 (0.04-23.00)** | **65** | **0.94 (0.04-4.80)** | **16** |

*****Where quantitative data for femoral blood available. Quantitative toxicology data on concentrations were available data in 81% of cases (80% of males and 84% of females). N/A: Not applicable

**Supplementary Table 1C: Median blood concentrations of MDMA by cause of death, Portugal***

| | All deaths | |
|---|---|---|
| | **Median mg/L(range)** | **Numbers*** |
| *Drug toxicity* | 0.84 (0.001-7.20) | 20 |
| Multiple drug toxicity | 0.77 (0.001-7.20) | 13 |
| MDMA toxicity | 0.97 (0.25-2.27) | 7 |
| *Other cause* | 0.60 (0.03-6.99) | 24 |
| **All Deaths** | **0.73 (0.001-7.20)** | **44** |

*****Where quantitative data available for blood concentrations. Quantitative toxicology data were available in 98% of cases.

**NB:** Insufficient data to show gender breakdown.

**Supplementary Table 1D: Median blood concentrations of MDMA by cause of death and gender, Turkey***

| | All deaths | | Males | | Females | |
|---|---|---|---|---|---|---|
| | **Median mg/L (range)** | **Numbers*** | **Median mg/L (range)** | **Numbers*** | **Median mg/L (range)** | **Numbers*** |
| *Drug toxicity* | 1.20 (0.03-28.00) | 179 | 1.19 (0.03-28.00) | 168 | 1.24 (0.20-13.95) | 11 |
| Multiple drug toxicity | 0.73 (0.03-28.00) | 77 | 0.71 (0.03-28.00) | 73 | 1.30 (0.20-4.31) | 4 |
| MDMA toxicity | 1.52 (0.26-17.40) | 102 | 1.52 (0.26-17.40) | 95 | 1.24 (0.55-13.95) | 7 |
| *Other cause* | 0.39 (0.02-9.32) | 92 | 0.39 (0.02-9.32) | 87 | 0.56 (0.23-5.39) | 5 |
| **All Deaths** | **0.82 (0.02-28.00)** | **271** | **0.81 (0.02-28.00)** | **255** | **1.00 (0.20-13.95)** | **16** |

***** Where quantitative data available for blood concentrations. Quantitative toxicology data were available in 25% of cases (21% of males and 19% of females).